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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,679	04/11/2001	RACHEL BAR-SHAVIT	108366	3009

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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/744,679	BAR-SHAVIT, RACHEL	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10-07-02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *3, 7, 8 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-6, 9-12, and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 16 is acknowledged. The traversal is on the ground(s) that the claimed methods and compositions of Group II-IV use antisense complementary to RNA encoding a protease activated receptor protein in the same family as the thrombin receptor of Group I and, therefore, a through search of the subject matter of Group I would encompass a search for the subject matter of Groups II-IV and that it would not constitute a serious burden to examine all of the claimed Groups. This is not found persuasive because the search for each of Groups II-IV would not be co-extensive. Antisense targeted to each of the different protease activated receptor proteins and associated methods, as claimed, would require a separate search because the antisense molecules have a different structure based on the sequence of the target gene and, further, have a different biological effect and mode of operation, by inhibiting a different target protein.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 7, 8, and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 16.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 6 and 16 are objected to because of the following informalities: Reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim" See MPEP

2173.05(s). Claims 6 and 16 should be amended to refer to the claimed sequences by SEQ ID NO:#. Appropriate correction is required.

Claim 4 is objected to because of the following informalities: the tense of "said tumor cell is" does not agree with the tense of "tumor cells" of claim 1. This objection would be obviated if claim 4 were amended to read, "said tumor cells are". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-6, 9-12, and 14-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9, 10 and 17 are indefinite due to the recitation "complementary". It is unclear whether complementary is meant to encompass sequences fully complementary to an RNA encoding PAR protein, or if complementary would also encompass sequences that are partially complementary, for example, sequences that have mismatches. Claims 2, 4-6, 11, 12, 14-16, 18 and 19 are indefinite for the same reasons due to dependence on claims 1, 9, 10 or 17.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-6, 10-12 and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1, 2, 4-6, 10-12 and 14-19 are drawn broadly to methods of treating any type of metastatic tumor cell in a subject *in vivo* (whole organism) using an antisense molecule targeted to a thrombin receptor, methods of treating any disorder involving the implantation of a placenta in a female patient using an antisense molecule targeted to a thrombin receptor, and pharmaceutical compositions comprising an antisense molecule targeted to a thrombin receptor.

The specification provides examples wherein a vector expressing an antisense cDNA of thrombin receptor was transfected into one metastatic breast cancer cell line and the cells showed a reduction in invasion in a matrigel assay. The specification does not demonstrate any correlation with the inhibition of cell invasion in cell culture and a reduction of metastasis in vivo in a subject. The specification demonstrates that there is

a temporal pattern of thrombin receptor mRNA expression in placental biopsies. The specification does not provide any examples wherein a disorder involving placental implantation is treated, nor wherein antisense targeted to thrombin receptor is used to modulate the expression of thrombin receptor in placental tissue in vivo or in vitro. The specification does not present any examples wherein antisense targeted to thrombin receptor was delivered to metastic cancer cells or placental cells *in vivo* (whole organism), nor wherein antisense targeted to thrombin receptor inhibited the expression of thrombin receptor mRNA in cells *in vivo* (whole organism). The specification does not provide any examples wherein treatment effects were obtained for metastatic tumor cells or a disorder involving the implantation of a placenta in a female subject. The specification has not provided any antisense composition what has pharmaceutical treatment effects, since these compositions are claimed as pharmaceutical compositions and would, therefore, require pharmaceutical properties, these claims have been included in this rejection.

At the time the instant invention was made, the therapeutic use of antisense oligonucleotides was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of antisense *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column,

second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed, or make a n antisense composition with pharmaceutical properties. The specification provides examples wherein antisense is delivered to cells *in vitro* and the invasion of metastatic cells is inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and

techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to thrombin receptor to generally any target metastatic cancer cell or tissue *in vivo* (whole organism) at a concentration effective to provide a pharmaceutical effect or deliver antisense to placental cells in vivo in a female subject. It is unclear whether successful delivery of antisense to placental cells would even provide a therapeutic effect for disorders involving implantation of a placenta. The specification indicates that thrombin receptor expression in placental tissue is temporal, yet there is no guidance on what particular times to regulate expression with antisense

to provide a therapeutic effect, or what degree of increase or decrease in expression is required. Although the specification provides a vague indication of when expression is increased or decreased in placental tissue which has been displaced from implantation, it is unclear whether antisense would also change thrombin receptor levels in the tissue of the female subject and how that would influence implantation.

In order to practice the invention claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in inhibition of the expression of thrombin receptor to a level sufficient to result in a pharmaceutical effect or to inhibit the metastatic potential of a cell in vivo or to provide a treatment for a disorder involving the implantation of a placenta in a female subject. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule *in vivo* and determine the temporal requirements of regulation of thrombin receptor in a placenta in vivo. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods of treatment claimed, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) methods of treatment using antisense, the lack of specific guidance for the *in vivo* (whole

organism) application of antisense methods of treatment for metastic cancer and placental implantation and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods of claims 1, 2, 4-6, 10-12 and 14-19 without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Schaeffer et al. (Clinical Pharmacology, Vol. 53, pages 487-491, 1997).

Schaeffer et al. disclose a phosphorothioate antisense oligonucleotide complementary to human thrombin receptor RNA (see for example, page 488, first column, first paragraph).

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Chaikof et al. (JBC, Vol 270, no 13, pages 7431-7436, Mar 13, 1995).

Chaikof et al. disclose antisense molecules that are complementary to sequences encoding thrombin receptors.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Mattson et al. (Amyloid, Vol. 3, No. 1, pages 28-40, 1996).

Mattson et al. disclose antisense oligonucleotides that are complementary to human thrombin receptor RNA.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Herbert et al. (J. Cellular Physiology 170:106-114, 1997).

Herbert et al. disclose an antisense oligonucleotide complementary to an RNA sequence of a thrombin receptor.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Even-Ram et al. (Nature Medicine, Vol. 4, No. 8, August 1998). Even-Ram et al. disclose a nucleotide sequence that is complementary to an RNA sequence of a protease activated receptor.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
December 16, 2002

KAREN LACOURCIERE
PATENT EXAMINER